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Transcriptional activation enhanced by the change in chromatin structure of mouse metallothionein-I promoter

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Metallothionein (MT) is a small, cysteine-rich protein active in zinc homeostasis, cadmium detoxification, and protection against reactive oxygen species. Mouse MT-I gene transcription is regulated by metal response element-binding transcription factor-1 (MTF-1), which is recruited to the promoter by zinc. We examined alterations in the chromatin structure of the MT-I promoter associated with enhanced transcriptional activation and effect of the alteration on the MT-I gene transcriptional activation. MTF-1 proved essential for zinc-induced epigenetic changes in the MT-I promoter. Chromatin immunoprecipitation assays demonstrated that zinc treatment rapidly decreased total histone H3 but not histone H3.3. Micrococcal nuclease sensitivity of the MT-I promoter was increased by zinc. Thus, the chromatin structure in the promoter may be locally disrupted by zinc-induced nucleosome removal. Without MTF-1 these changes were not observed, and an MTF-1 deletion mutant recruited to the MT-I promoter by zinc that did not recruit the coactivator p300 or activate MT-I transcription did not affect histone H3 in the MT-I promoter in response to zinc. Interleukin-6, which induces MT-I transcription independently of MTF-1, did not reduce histone H3 levels in the promoter. Rapid disruption of nucleosome structure at the MT-I promoter is mediated by zinc-responsive recruitment of an active MTF-1-coactivator complex. Furthermore, when zinc was removed, the chromatin did not rapidly revert to its resting state. We also demonstrated that nucleosome-disrupted MT-I promoter showed enhanced transcriptional activation. The exclusion of the histone might act as a memory of the first zinc-induced MT-I transcription.

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Neurobehavioural effects of brilliant blue FCF in two-generation toxicity study in mice

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[PURPOSE] The present study was designed to evaluate reproductive and neurobehavioural effects of brilliant blue FCF in mice throughout two generations.

[METHODS] Brilliant blue FCF was given to mice in the diet at levels of 0 (control), 0.08%, 0.24%, and 0.72% from 5 weeks of age of the F0 generation to 11 weeks of age of the F1 generation, and selected reproductive and neurobehavioural parameters were measured.

[RESULTS] In exploratory behaviour of adult females of the F0 generation, movement time (s) showed a significant tendency to be increased and average time of rearing (s) showed a significant tendency to be decreased in the treatment groups. In the F1 generation, surface righting at postnatal day (PND) 4 was affected significantly in male and female offspring in a dose-related manner. In exploratory behaviour of adult females of the F1 generation, number of horizontal activities showed a significant tendency to be decreased in the treatment groups. After weaning, the body weight gain of females was significantly affected during 10–11 weeks of age in a dose-related manner.

[CONCLUSION] In the present study, brilliant blue FCF showed a few significant adverse effects on neurobehavioural parameters. The high dose level was based on the current ADI of brilliant blue FCF. The actual dietary intake of brilliant blue FCF in Japan is presumed to be much lower approximately 0.28–0.56 μg/kg/day. It would therefore appear that the levels of actual dietary intake of brilliant blue FCF are unlikely to produce any adverse effects in humans.